K010668

JUL - 5 2001

Bayer Diagnostics

ASC:180 and ADVIA Centaur Rubella IgM assay

Summary of Safety and Effectiveness

As required by 21 CFR 807.92, the following 510(k) Summary is provided:

1. Submitter Information

Contact person:	William J. Pignato
Address: 63 North Street Medfield, MA 02052	Bayer Diagnostics Corporation
Phone:	(508) 359-3825
FAX:	(508) 359-3356
e-mail:	william.pignato.b@bayer.com

Date Summary Prepared:	January 19, 2001

2. Device Information

Proprietary Name:	ADVIA Centaur Rubella IgM assay
Common Name:	A chemiluminescence tests for the determination of IgM antibodies to the rubella virus
Classification Name:	Rubella Virus Serological Reagent
Class:	Class II
CFR:	21 CFR 866.3510
Product Code:	LFX

3. Predicate Device Information

Name:	AxSym Rubella IgM Antibody Assay IMx Rubella IgM Antibody Assay
Manufacturer:	Abbott Laboratories One Abbott Park Road Abbott Park, IL 60064

4. Device Description

Rubella virus is a member of the togaviridae family. It is a teratogenic virus that can be passed transplacentally from the infected mother to the fetus and can lead to fetal death or congenital rubella syndrome (CRS). The risk of fetal infection is greatest during the first trimester of pregnancy.

Neonates born with CRS may exhibit one or more of the following symptoms: low birth weight, deafness, eye disease, mental retardation, and cardiac abnormalities.
A primary infection induces an IgM and an IgG response. Within 4 to 6 months, IgM levels become undetectable or very low. IgG decreases to low levels, but lasts indefinitely and confers lifelong immunity. A secondary infection exhibits a rising IgG antibody without significant rise in levels of IgM.[1] Therefore, testing for IgM antibodies to rubella virus is a useful aid in the diagnosis of acute infection.
Only one serological type of rubella virus is found in the population[2, 3] and since the introduction of the rubella vaccine in the late 1960s, the incidence of CRS has dropped dramatically. However, outbreaks of rubella still occur and pose a potential risk to women of childbearing age.

5. Statement of Intended Use

The ADVIA Centaur Rubella IgM assay is an IgM antibody capture microparticle direct chemiluminometric in vitro diagnostic immunoassay for the qualitative detection of IgM antibodies to the rubella virus in serum or plasma (EDTA, heparin) as an aid in the presumptive diagnosis of current or recent infection with rubella.

6. Summary of Technological Characteristics

The ADVIA Centaur Rubella M assay is a sandwich immunoassay using direct, chemiluminometric technology. The anti-human IgM_{Fc} monoclonal antibody is covalently coupled to paramagnetic particles in the Solid Phase. In the Lite Reagent, the rubella virus antigen is labeled with acridinium ester. Antibody-antigen complexes will form if rubella IgM is present in the sample.

A direct relationship exists between the amount of rubella IgM activity present in the patient sample and the amount of relative light units (RLUs) detected by the system. A result of positive or negative is determined according to the Cutoff Index Value established with the calibrators.

7. Performance Data

Non-clinical

Limitations

- The ADVIA Centaur Rubella M assay is limited to the detection of IgM antibodies to rubella virus in human serum or plasma.
- Specimens taken early during the acute phase of infection may not contain detectable levels of IgM antibody to rubella virus. A negative result for IgM antibodies to rubella virus does not preclude a recent primary infection.
- In the absence of clinical symptoms or known exposure, a diagnosis of a primary rubella infection should not be based on a positive result alone. The specimen should be confirmed using another method before making the diagnosis.
- Do not use heat inactivated specimens.
- Do not use specimens with obvious microbial contamination.
- The performance of the ADVIA Centaur Rubella M assay has not been established with cord blood, neonatal specimens, cadaver specimens, or body fluids other than serum or plasma, such as saliva, urine, amniotic, or pleural fluids.
- The performance of the assay has not been established for populations of immunocompromised or immunosuppressed patients.

Serum specimens that are . . .	*Demonstrate ≤ 10% in results up to . . .*
hemolyzed	500 mg/dL of hemoglobin
lipemic	1000 mg/dL of triglycerides
icteric	60 mg/dL of conjugated bilirubin 40 mg/dL of unconjugated bilirubin
proteinemic	3 g/dL of protein
hyper IgM	3 mg/mL of immunoglobulin M

Expected Values

The incidence of IgM antibody to the rubella virus varies among populations. Data was obtained on 950 samples from prenatal women and random individuals. Of these samples, 11 (1.1%) were positive, 12 (1.3%) were equivocal, and 927 (97.6%) were negative.
As with all in vitro diagnostic assays, each laboratory should determine its own reference range(s) for the diagnostic evaluation of patient results.

Population	*N*	*Negative*	*Equivocal*	*Positive*
Prenatal women	585	576 (98.4%)	5 (0.9%)	4 (0.7%)
Random individuals	365	351 (96.2%)	7 (1.9%)	7 (1.9%)

Performance Characteristics

Sensitivity and Specificity

Relative Agreement

The presence of rubella IgM antibody in 1054 frozen and fresh specimens was evaluated at three U.S. sites using the ADVIA Centaur Rubella M assay and a commercially available rubella IgM EIA. Prenatal, random hospital, and clinical specimens were obtained from the mid-Atlantic and Midwest regions of the United States as well as Canada and Germany. Of the 1054 specimens tested, 13 were equivocal by the ADVIA Centaur Rubella M assay. Discordant results were found on 18 specimens. Further testing was done on the discordant samples using other commercially available tests for rubella IgM.

Relative Sensitivity

Using the alternative method, 112/1054 tested positive for rubella IgM antibody. Of the specimens that tested positive, 1 was equivocal, 101 were positive, and 10 were negative using the ADVIA Centaur Rubella M assay. The relative sensitivity was 91.0%.

Relative Specificity

Using the alternative method, 932/1054 tested negative for rubella IgM antibody. Of the specimens that tested negative, 11 were equivocal, 913 were negative, and 8 were positive using the ADVIA Centaur Rubella M assay. The relative specificity was 99.1%.
NOTE: Samples giving equivocal results were not included in the calculation of relative sensitivity, relative specificity, and relative agreement.

Relative Sensitivity, Specificity, and Agreement Before Resolution of Discordant Samples

Site	*N*	*Relative Sensitivity (%)*	*Relative Specificity (%)*	*Relative Agreement (%)*
1	300	92.3 (48/52)	99.6 (242/243)	98.3 (290/295)
2	377	85.3 (29/34)	99.8 (335/336)	98.4 (364/370)
3	377	96.0 (24/25)	98.3 (336/342)	98.1 (360/367)
Total	1054	91.0 (101/111)	99.1 (913/921)	98.3 (1014/1032)

		Rubella IgM EIA			
		Positive	Equivocal	Negative	Total
ADVIA Centaur Rubella M	Positive	101	2	8	111
	Equivocal	1	1	11	13
	Negative	10	7	913	930
	Total	112	10	932	1054

Relative sensitivity = 90.99% (101/111) 95% Confidence Limits 84.06 – 95.59
Relative specificity = 99.13% (913/921) 95% Confidence Limits 98.30 – 99.62
Relative agreement = 98.26% (1014/1032) 95% Confidence Limits 97.26 – 98.96

Consensus Testing

Further analysis of the eighteen specimens with discordant results was performed using an additional commercially available EIA for rubella IgM. Of the ten samples that were negative by ADVIA Centaur and positive by EIA, one was equivocal, three were positive, and six were negative by consensus. Of the eight that were positive by ADVIA Centaur and negative by EIA, two were positive and 6 were negative by consensus. Two of the six negative consensus specimens were positive by clinical symptoms and other methodology.

Precision

Reproducibility of the ADVIA Centaur Rubella M assay was determined as described in NCCLS protocol EP5-T2.[8] A sixteen member panel of serum and plasma was assayed two times in two separate daily runs, over a period of 20 days (n = 80). The following results were obtained using one reagent lot and a stored calibration curve:

Panel Member	Sample Type	N	Mean Concentration (Index)	Within-run		Total**	
				SD	% CV	SD	% CV
	Negative Control	80	0.18	0.04	NA*	0.07	NA
	Positive Control	80	1.16	0.04	3.4	0.06	5.5
1	Serum	80	0.21	0.04	NA	0.06	NA
2	EDTA	80	0.19	0.04	NA	0.07	NA
3	Heparin	80	0.19	0.04	NA	0.07	NA
4	Sodium citrate	80	0.18	0.04	NA	0.08	NA
5	Serum	80	1.04	0.04	4.3	0.07	6.3
6	EDTA	80	1.07	0.05	4.9	0.07	6.2
7	Heparin	80	1.04	0.04	4.2	0.06	6.2
8	Sodium citrate	80	1.10	0.03	2.9	0.06	5.5
9	Serum	80	1.13	0.04	3.7	0.06	5.5
10	EDTA	80	1.17	0.04	3.2	0.06	5.1
11	Heparin	80	1.16	0.04	3.7	0.07	5.8
12	Sodium citrate	80	1.21	0.04	3.3	0.06	4.9
13	Serum	80	2.21	0.07	3.4	0.11	5.1
14	EDTA	80	2.23	0.08	3.5	0.11	5.0
15	Heparin	80	2.27	0.08	3.4	0.13	5.5
16	Sodium citrate	80	2.37	0.06	2.7	0.12	5.2

* NA = Not Applicable.

** Includes within-run and run-to-run.

System reproducibility was determined by testing a 4 member panel with 3 reagent lots including 5 instruments and 3 sites over multiple days. The panel was assayed 3 times in each of 55 runs. The following results were obtained:

Panel Member	N	Mean Index Value	Within-run		Total**	
			SD	% CV	SD	% CV
Negative Control	171	0.31	0.06	NA*	0.07	NA
Positive Control	171	1.54	0.06	5.22	0.11	7.58
1	170	0.33	0.06	NA	0.07	NA
2	171	1.47	0.09	6.00	0.11	7.58
3	171	1.92	0.08	3.98	0.09	5.60
4	168	2.65	0.23	4.21	0.16	6.20

* NA = Not Applicable.

** Includes within-run and run-to-run.

The reproducibility was also calculated for each individual site with each panel member. The following table summarizes the precision of three sites:

Rubella IgM Precision Summary by Site

Panel Member	Site Code	N	Mean Concentration (Index Value)	Within-Run D	Within-Run % CV	Total** D	Total** CV
Negative	1	141	0.30	0.06	NA*	0.07	NA
Negative	2	15	0.45	0.07	NA	0.08	NA
Negative	3	15	0.33	0.04	NA	0.05	NA
Positive	1	141	1.54	0.06	4.2	0.09	5.8
Positive	2	15	1.59	0.08	5.2	0.09	5.5
Positive	3	15	1.51	0.05	3.1	0.06	3.9
1	1	140	0.31	0.06	NA	0.07	NA
1	2	15	0.50	0.09	NA	0.11	NA
1	3	15	0.36	0.02	NA	0.02	NA
2	1	141	1.44	0.09	6.5	0.12	8.1
2	2	15	1.66	0.07	4.4	0.09	5.6
2	3	15	1.57	0.04	2.8	0.08	5.1
3	1	141	1.90	0.08	4.1	0.12	6.3
3	2	15	2.07	0.07	3.3	0.09	4.4
3	3	15	1.95	0.07	3.4	0.13	6.4
4	1	141	2.60	0.11	4.4	0.17	6.6
4	2	12	2.93	0.10	3.4	0.10	3.4
4	3	15	2.87	0.09	3.2	0.12	4.3

Evaluation of Potential Interfering Disease States

To further evaluate the specificity of the ADVIA Centaur Rubella M assay, 107 specimens from individuals with the various disease states were tested. The rubella IgM status of the specimens was confirmed using an alternate method. The results are shown in the following table:

Disease State	*Rubella IgM Status by Alternate Method*	*ADVIA Centaur Rubella M Assay Result*	
		< 1.00 Index Value	*≥ 1.00 Index Value*
Cytomegalovirus	Negative	9	0
	Positive	0	1
Epstein-Barr virus	Negative	9	0
	Positive	0	0
Herpes simplex virus	Negative	10	0
	Positive	0	0
Influenza vacinees	Negative	10	0
	Positive	0	0
Measles virus	Negative	4	0
	Positive	0	6
Parvovirus B19	Negative	10	0
	Positive	0	0
Syphilis	Negative	10	0
	Positive	0	0
Varicella zoster virus	Negative	8	0
	Positive	0	0
Multiple myeloma	Negative	10	0
	Positive	0	0
Rheumatoid factor	Negative	10	0
	Positive	0	0
ANA	Negative	10	0
	Positive	0	0

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

JUL - 5 2001

Mr. William J. Pignato
Director of Regulatory Affairs
Bayer Diagnostics Corporation
63 North Street
Medfield, MA 02052-1688

Re: 510(K) Number: K010668
Trade/Device Name: Bayer Diagnostics ADVIA Centaur Rubella IgM Assay
Regulation Number: 866.3510
Regulatory Class: II
Product Code: LFX
Dated: May 16, 2001
Received: May 18, 2001

Dear Mr. Pignato:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number (if known): K010668

Device Name: Bayer Diagnostics ADVIA Centaur Rubella IgM Assay

The ADVIA Centaur Rubella IgM assay is an IgM antibody capture microparticle direct chemiluminometric in vitro diagnostic immunoassay for the qualitative detection of IgM antibodies to the rubella virus in serum or plasma (EDTA, heparin) as an aid in the presumptive diagnosis of current or recent infection with rubella.

Woodley Dubois

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K010668

(PLEASE DO NOT WRITE BELOW THIS LINE--CONTINUE ON ANOTHER PAGE, IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use X OR Over-The-Counter Use _____

(Per 21 CFR 801.109)